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Long-acting bronchodilation with once-daily dosing of tiotropium (Spiriva) in stable chronic obstructive pulmonary disease.

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Tiotropium (Spiriva; Ba679BR) is a new-generation, long-acting anticholinergic bronchodilator that has muscarinic M(1) and M(3) receptor subtype selectivity. A multicenter, randomized, double-blind, parallel group, placebo-controlled study was conducted to evaluate the dose-response characteristics of tiotropium inhalation powder given once daily to stable patients with chronic obstructive pulmonary disease (COPD). Patients (mean FEV(1) = 1.08 L [42% predicted]) were randomized to receive 0, 4.5, 9, 18, or 36 microg tiotropium once daily at noon for 4 wk, with spirometry done before and hourly for 6 h after dosing. Patients measured and recorded their peak expiratory flow rates (PEFRs) three times each day. Significant dose-related improvement in FEV(1) and significant improvement in FVC occurred within 1 h after the first dose of tiotropium as compared with placebo. Over the 29 d of the study, all doses of tiotropium produced significant increases over placebo in trough (i.e., as measured spirometrically at 20 to 24 h after the previous dose and just before the next dose of tiotropium), peak, and 6-h postdose average FEV(1) and FVC, and in PEFR, without a significant difference among the different doses investigated. PEFR gradually returned to pretreatment baseline levels over a 3-wk evaluation period following the discontinuation of tiotropium. The overall safety profile for the tiotropium doses was similar to that for placebo. In summary, tiotropium was shown to be safe and effective in doses ranging from 4.5 to 36 microg delivered once daily. The improvements in spirometry with once-daily dosing confirm the long duration of action of tiotropium reported in single-dose studies, and its sustained improvement of spirometric measures over the 1 mo of testing in the study points to utility of tiotropium as a maintenance bronchodilator for patients with COPD. On the basis of the comparable bronchodilator response at doses from 9 to 36 microg, and advantages suggested by the safety profile at doses below 36 microg in this study, a dose of 18 microg once daily was selected for use in long-term studies of the safety and efficacy of tiotropium.

Publication Types:
- Clinical Trial
- Multicenter Study
- Randomized Controlled Trial

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Pulmonary delivery of a dopamine D-1 agonist, ABT-431, in dogs and humans

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Abstract

The purpose of this study was to evaluate the feasibility of intrapulmonary delivery of ABT-431, a selective D1 receptor agonist. Following intratracheal instillation of the drug solution, the lung bioavailability was found to be approximately 75% in dogs. An aerosol suspension formulation was then developed by dispersing the drug in tetrafluoroethane, HFC-134a, with the aid of poloxamer 124 and vitamin E. This ABT-431 MDI aerosol formulation showed about 40% of the particles emitted from the valve and actuator system to be under 5 μm in diameter. Also, the primary package (15 mL aluminum container, DF10/ACT-150 valve, and Micron-4-actuator with the orifice 0.4 mm) was satisfactory for accurate and reproducible dosimetry. Using tracheostomized beagle dogs, the C_{max} following tracheal administration of 5 mg aerosolized ABT-431 was found to be 13.3±0.9 ng ml^{-1} and the AUC_{0-24} was estimated at 33.2±10.6 h ng ml^{-1}. The lung bioavailability of the aerosolized drug was 34% compared to intravenous injection in dogs. In humans, results from a single rising dose study demonstrated that rapid absorption of ABT-431 following oral inhalation administration resulted in a dose-dependent increase in the area under the plasma-time curve at dosage levels between 3.3 and 13.2 mg. There is a possibility of up to 25% absorption of the drug from human lung. Thus, pulmonary bioavailability of ABT-431 is significantly greater than that of oral administration. Also, these findings suggest that small and lipophilic

compounds, especially with hepatic first pass effect, may be effectively delivered systemically using oral inhalation aerosols.

Author Keywords: Dopamine D-1; Agonist; ABT-431; Metered-dose inhalation; Pulmonary absorption; Pulmonary bioavailability

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